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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/516,478	06/27/2005	Jonathan M. Lee	PTQ-0065	2533

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EXAMINER	
AEDER, SEAN E	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 07/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/516,478	LEE, JONATHAN M.	
	Examiner	Art Unit	
	Sean E. Aeder, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) *7-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Action

The Election filed 6/5/06 in response to the Office Action of 5/4/06 is acknowledged and has been entered. Applicant elected group III, drawn to a method comprising measuring EEF1A2 *protein* levels for diagnosing, prognosticating, and selecting an effective treatment for cancer, and the species "breast cancer" with traverse.

The traversal is on the ground(s) that a search and examination of all of the inventions would not impose a serious burden on the examiner since a search of the prior art relating to claims 1-30 has been performed in the PCT application. Further, Applicant states that the Examiner has not provided evidence to support that the groups have acquired separate status in the art. Further, Applicant traverses the species requirement on the grounds that in accordance with MPEP 808.01, an election of species should be made when a generic claim recites such a multiplicity of species that an unduly extensive and burdensome search is required. In the instant case, Applicant argues that the generic claim is not drawn to such a large multiplicity that search of all species of cancers would be unduly extensive or burdensome. Applicant further argues that a search of the generic claim should reveal any art relating to various cancer types. Applicant further argues that the lack of unity outlined in the restriction requirement of 5/4/06 contradicts the Search Report and the Written Opinion issue in the Canadian PCT application of which this case is a U.S. National Stage. Applicant further disagrees that the technical feature linking Groups I-XIII is a EEF1A2 gene, rather Applicant asserts that the technical feature linking Groups I-XIII is inventor's *recognition* for the

first time that expression of EEF1A2 gene is associated with and can confer oncogenic properties on a cell including enhancing focus formation, allowing anchorage independent growth and increasing doubling time of fibroblasts, promoting in vivo tumorigenicity in fibroblasts and increasing the growth rate and in vivo tumorigenicity of carcinoma cells. Applicant states that this technical feature is neither taught nor suggested by Lund et al. This is not found persuasive. At the outset, it is noted that the instant application is a national stage entry of a PCT, filed under 371 and not 111. As such, the instant application was restricted in accordance with PCT Rule 13.1. Further, it is noted that MPEP 802.01 provides that restriction is proper between inventions which are independent or distinct. Each of the groups outlined in the restriction include distinct methods of diagnosing and prognosticating, distinct kits, distinct methods of treating, and distinct methods of screening. Each of the method inventions is further unrelated, as they comprise distinct steps and utilize different products, which demonstrates that each method has a different mode of operation. Searching and examining each of these methods would result in a serious burden on the examiner. Further, each of the product inventions are unrelated because each are made by materially different methods, and are used in materially different methods which have different modes of operation, different functions and different effects. Furthermore, it is noted that the literature search, particularly relevant in this art, is not coextensive and is very important in evaluating the burden of search. Different searches and patentability issues, which were not addressed in the PCT search, are involved in the examination of each group. Further, it is noted that the species requirement is proper since the species

do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical feature for the following reasons: Each species represent separate and distinct cell types with different morphologies and functions such that one species could not be interchanged with the other. Further, each species requires a divergent search and searching all the species together would be unduly burdensome. As set forth in the Office Action of 5/4/06, the application contains fifteen groups of inventions, which are not so linked to form a single general inventive concept under PCT Rule 13.1. It is unclear why the Canadian Examiner did not issue a lack of unity restriction requirement for the Canadian PCT. As stated in the Office Action of 5/4/06, the Examiner has determined that the technical feature linking the groups appeared to be the EEF1A2 gene, rather than some kind of "recognition" that expression of EEF1A2 gene is associated with and can confer oncogenic properties on a cell including enhancing focus formation, allowing anchorage independent growth and increasing doubling time of fibroblasts, promoting in vivo tumorigenicity in fibroblasts and increasing the growth rate and in vivo tumorigenicity of carcinoma cells, as asserted in the Response of 6/5/06. It is noted that a "recognition" is not a technical feature. Further, it is noted that the recognized attributes described in the Response of 6/5/06 are all linked by the technical feature of the EEF1A2 gene, which is not a *special* technical feature as defined by PCT Rule 13.2 (see Lund et al; Genomics, 1996, 36:359-361). For these reasons the restriction requirement is deemed to be proper and is therefore made FINAL.

Claims 1-30 are pending.

Claim 7-30 are withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to a non-elected invention.

Claims 1-6 are currently under consideration.

Claim Objections

Claims 1 and 4 are objected to for reciting unelected inventions of groups I (methods drawn to measuring EEF1A2 gene amplification), II (methods drawn to measuring EEF1A2 mRNA levels), and IV (methods drawn to measuring EEF1A2 protein activity). Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 4 and dependent claims 2, 3, 5, and 6 are rejected for being vague and indefinite because claims 1 and 4 recite the term EEF1A2 as the sole means of identifying the polypeptide of the claimed method. The use of laboratory designations only to identify a particular molecule renders the claims indefinite because different laboratories may use the same laboratory designations to define completely distinct

molecules. Amending the claims to specifically and uniquely identify EEF1A2 by a SEQ ID NO can obviate the rejection.

Claim 1 and dependant claims 2-3 are rejected because claim 1 is indefinite for reciting methods of comparing EEF1A2 protein levels in a biological sample to those of "a control", wherein an increase in EEF1A2 protein levels in the biological sample as compared to the control is indicative of breast cancer. The specification discloses that "a control" is any sample obtained from an individual known not to have cancer, any sample obtained previously from the subject prior to the onset or suspicion of cancer, or any standard from data obtained from a data bank corresponding to currently accepted normal levels of this gene or gene product (page 18, in particular). However, the claims do not distinctly *recite* what is meant by "a control". For example, the claims do not *recite* from which type of tissue "a control" is derived.

Claim 4 and dependent claims 5-6 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. Claim 4 recites a method for prognosticating survival and selecting an effective treatment regime for a patient suffering from breast cancer comprising measuring EEF1A2 protein levels from a biological sample obtained from said patient; however, it is unclear what kind of measurement would be indicative of what kind of prognosis or what kind of measurement would result in what type of

selection. Thus, there are missing step involving correlating a measurement to a prognosis and correlating a measurement to a selection. See MPEP § 2172.01.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for diagnosing breast cancer comprising measuring EEF1A2 protein level in breast tissue sample from a patient and comparing said EEF1A2 protein level to the level of EEF1A2 protein in a control breast tissue sample from an individual known not to have cancer wherein an increase in EEF1A2 protein level in the sample from the patient as compared to the level of the control sample is indicative of the patient having breast cancer, does not reasonably provide enablement for a method for diagnosing every type of cancer comprising measuring EEF1A2 protein level in any type of biological sample from a patient and comparing said protein level to the level of EEF1A2 protein level in any type of control. Further the specification does not reasonably provide enablement for a method for prognosticating survival or selecting an effective treatment regime for any patient suffering from any cancer comprising measuring EEF1A2 protein levels in any type of biological sample. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in *Ex parte* Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The instant claims are broadly drawn to a method for diagnosing every type of cancer comprising measuring EEF1A2 protein level in any type of biological sample from a patient and comparing said protein level to the level of EEF1A2 protein level in any type of control (see claims 1-3). The claims are further broadly drawn to a method for prognosticating survival and selecting an effective treatment regime for any patient suffering from any cancer comprising measuring EEF1A2 protein levels in any type of biological sample (see claims 4-6).

The specification teaches that EEF1A2 *RNA* is undetectable in normal breast tissue, but 2 out of 6 primary human breast tumors had readily detectable EEF1A2 *RNA* expression (page 6, in particular). The specification further states that increased EEF1A2 *RNA* in primary tumors implicates EEF1A2 in breast cancer development (page 6, in particular). Further, the specification *prophetically* states that antibodies that specifically recognize EEF1A2 protein can be generated and used to stain samples of tumor removed from ovarian cancer or breast cancer patients (see page 17, in particular). The specification further *prophetically* states that patients with tumor

samples that are positive for EEF1A2 are expected to survive for a shorter period of time as compared to patients with tumor samples negative for EEF1A2 (page 17, in particular). The specification further *prophetically* states that prognostic information relating to EEF1A2 protein expression can be used to enhance clinical decision-making and to select appropriate treatment regimes (page 17, in particular). The specification further *prophetically* states that increased EEF1A2 expression in tumors of a subject is expected to lead to increased EEF1A2 protein levels in biological samples such as plasma, serum, and other tissue samples from said subject (page 18, in particular). It is noted that the specification provides no working examples demonstrating that methods comprising measuring EEF1A2 protein levels would diagnose breast cancer with any predictability of success. Further it is noted that the specification provides no working examples demonstrating that methods comprising measuring EEF1A2 protein levels would predictably prognosticate survival of breast cancer patients. Further, it is noted that the specification provides no working examples demonstrating that methods comprising measuring EEF1A2 protein levels would predictably help one select an effective treatment for a breast cancer patient.

In the art, Tomlinson et al (BMC Cancer, 9/12/05, 5:113, pages 1-7) teaches an immunohistochemistry-based method for diagnosing breast cancer comprising measuring EEF1A2 protein level in breast tissue sample from a patient and comparing said protein level to the level of EEF1A2 protein in a control breast tissue sample from an individual known not to have cancer (see figure 3, in particular). Tomlinson et al

does not teach methods of prognosticating survival of breast cancer patients or methods of selecting an effective treatment for a breast cancer patient

The state of the prior art dictates that if a molecule such as EEF1A2 is to be used as a surrogate for a diseased state, some disease state must be identified in some way with the molecule. There must be some expression pattern that would allow the claimed polypeptide to be used in a diagnostic or prognostic manner. For example, Tockman et al (Cancer Res., 1992, 52:2711s-2718s) teach considerations necessary in bringing a cancer biomarker (intermediate end point marker) to successful clinical application. Tockman et al teaches that prior to the successful application of newly described diagnostic and prognostic markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence and confirm marker predictive value in prospective population trials (see abstract). Early stage markers of carcinogenesis have clear biological plausibility as markers of preclinical cancer and if validated (emphasis added) can be used for population screening (p. 2713s, col 1). The reference further teaches that once selected, the sensitivity and specificity of the biomarker must be validated to a known (histology/cytology-confirmed) cancer outcome. The essential element of the validation of an early detection marker is the ability to test the marker on clinical material obtained from subjects monitored in advance of clinical cancer and *link* those marker results with subsequent histological confirmation of disease. This irrefutable link between antecedent marker and subsequent acknowledged disease is the essence of a valid intermediate end point marker (p. 2714, see Biomarker Validation against

Acknowledged Disease End Points). Clearly, prior to the successful application of newly described markers, markers must be validated against acknowledged disease end points and the marker predictive value must be confirmed in prospective population trials (p. 2716s, col 2). Therefore, absent evidence of the protein's expression including the correlation to a diseased state, one of skill in the art would not be able to predictably use the peptides in any diagnostic or prognostic setting without undue experimentation.

Further, it is noted that the specification describes experiments examining EEF1A2 mRNA levels. Those of skill in the art recognize that over expression of a particular nucleic acid specific for a tissue type, does not necessarily correlate nor predict equivalent levels of polypeptide expression. There are many steps in the pathway leading from DNA to protein, and all of them can, in principle, be regulated. For example, Alberts *et al.* (Molecular Biology of the Cell, 3rd edition, 1994, page 465) illustrate post-transcriptional regulation of ferritin wherein the translation of ferritin mRNA into ferritin polypeptide is blocked during periods of iron starvation. Likewise, if excess iron is available, the transferrin receptor mRNA is degraded and no transferin receptor polypeptide is translated. Lewin, B. also teaches (Genes VI, Oxford University Press, Inc., NY, Chapter 29, 1997) that a major control point for genes exists during the initiation of transcription by the interaction of the RNA polymerase with its promoter. Concurring with Alberts *et al.*, Lewin further acknowledges downstream control of gene expression since translation of mRNA in the cytoplasm is also a point of control. Also, with regards to tumor associated antigens, Fu et al (EMBO Journal, 1996, Vol. 15, pp. 4392-4401) teach that levels of p53 protein expression do not correlate with levels of

p53 mRNA levels in blast cells taken from patients with acute myelogenous leukemia, said patients being without mutations in the p53 gene. Furthermore, Mallampalli *et al.* (Biochem. J. Vol. 318, 1996, pages 333-341) teach that the glucocorticoid, betamethasone, increased mRNA expression of cholinephosphate cytidylyltransferase (CT) as determined by RT-PCR and Southern analysis, but did not alter the levels of the CT enzyme as assayed by Western blotting (abstract, and page 339, 2nd column, 2nd paragraph). Finally, Lewin acknowledges that control of gene expression can occur at multiple stages and that production of RNA *cannot inevitably* be equated with production of protein. Thus, the predictability of protein translation is not necessarily contingent on the levels of mRNA expression due to the multitude of homeostatic factors affecting transcription and translation. Thus, information obtained from various expression profiles in both normal and diseased tissue only serves as the basis for further research on the observation itself.

The level of unpredictability for the detection of any disease is quite high. Since neither the specification nor the art provide evidence of a universal association between the claimed diagnostic method and every type of cancer using every type of sample, a practitioner wishing to practice said diagnostic method would be required to provide extensive experimentation to demonstrate such an association. Such experimentation would in itself be inventive. Further, the level of unpredictability for prognosticating a patient with any disease and methods of determining effective treatments is quite high. Since neither the specification nor the art provide evidence demonstrating that methods of measuring EEF1A2 protein levels in any type of patient sample would predictably

prognosticate survival of any patient or would predictably help one select an effective treatment for any patient, a practitioner wishing to practice said prognostication or selection would be required to provide extensive experimentation to demonstrate an association between EEF1A2 protein levels and patient survival and an association between EEF1A2 protein levels and effective treatment selections. Such experimentation would in itself be inventive.

One cannot extrapolate the teachings of the specification to the scope of the claims because the claims are broadly drawn to a method for diagnosing every type of cancer comprising measuring EEF1A2 protein level in any type of biological sample from a patient and comparing said protein level to the level of EEF1A2 protein level in any type of control, and Applicant has not enabled said method because it has not been shown that one would predictably diagnose every type of cancer with a method comprising measuring EEF1A2 protein level in any type of biological sample from a patient and comparing said protein level to the level of EEF1A2 protein level in any type of control. Further, one cannot extrapolate the teachings of the specification to the scope of the claims because the claims are broadly drawn to a method for prognosticating survival and a method for selecting an effective treatment regime for any patient suffering from any cancer comprising measuring EEF1A2 protein levels in any type of biological sample, and Applicant has not enabled said methods because it has not been shown that one would be able to predictably prognosticate survival for any patient suffering from any type of cancer or predictably select an effective treatment

regime for any patient suffering from any cancer comprising a method of measuring EEF1A2 protein levels.

In view of the teachings above and the lack of guidance, workable examples and or exemplification in the specification, it would require undue experimentation by one of skill in the art to determine with any predictability, that the methods would function as claimed.

Summary

No claim is allowed. Claims 1-6 are rejected under 35 U.S.C. 112, first paragraph, but free of the prior art teaching methods drawn to diagnosis, prognosis, and treatment selection comprising detecting EEF1A2 protein. The closest prior art for claims 1-6 is Ruest et al (Journal of Biological Chemistry, 2/15/02, 277(7):5418-5425), which teaches an EEF1A2-mediated protective effect against caspase 3-mediated apoptosis in cultured myotubes; however, this reference does not teach or suggest methods drawn to diagnosis, prognosis, and treatment selection comprising detecting EEF1A2 protein.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sean E. Aeder, Ph.D. whose telephone number is 571-272-8787. The examiner can normally be reached on M-F: 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SEA

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